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An efficient activation of the hydroxyl function by (diethylamino)sulfur trifluoride (DAST): preparation of chiral polyoxygenated tetrahydrofurans by stereoselective benzyloxy group participation

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Summary — Based on an intramolecular benzyloxy or amide group participation, two sets of experimental conditions have been established for the preparation of *cis/trans* tetrahydrofurans **6** or lactone **8** from sugar-derived open-chain hydroxylated precursors **4**. These include: (1) a two-step mesylation–cyclization promoted by LiOH/THF–H_2O or NaI/CH_3CN at reflux; or (2) a one-step cyclization mediated by (diethylamino)sulfur trifluoride (DAST) at −78 °C in CH_2Cl_2. The scope and limitations of these cyclizations are described particularly in relation to a stereoselective synthesis of highly oxygenated chiral tetrahydrofurans. Molecular modeling studies tentatively rationalized our experimental cyclization results affording five-membered versus six-membered heterocycles starting from different precursors.

polyoxygenated tetrahydrofuran / (diethylamino)sulfur trifluoride (DAST) / benzyl group participation / amide group participation / L-gulonolactone / differentially protected 1,4-diol

Résumé — Activation efficace de la fonction hydroxyle par le diéthylaminotrifluorosulfurane (DAST): préparation de tétrahydrofuranes polyoxygénés chiraux par participation stéréosélective de groupements benzyloxy. Basées sur une réaction de participation intramoléculaire de groupements benzyloxy ou amide, deux séries de conditions expérimentales ont été respectivement mises au point pour la préparation des tétrahydrofuranes polyoxygénés de type **6** ou de la lactone **8** à partir des polyols acycliques précurseurs dérivés de sucres de type **4**. Ces procédés décrivent une séquence réactionnelle en deux étapes de mésylation–cyclisation induite par les systèmes LiOH/THF–H_2O ou NaI/CH_3CN au reflux ou une cyclisation en une étape assistée par le diéthylaminotrifluorosulfurane (DAST) à −78 °C dans le dichlorométhane. Ces cyclisations sont rapportées en considérant plus particulièrement la synthèse stéréosélective de tétrahydrofuranes chiraux polyoxygénés. Des études de modélisation moléculaire ont été réalisées pour essayer de rationaliser les résultats de cyclisation observés impliquant les participations des groupements benzyloxy ou amide pour différents précurseurs de cyclisation.

tétrahydrofurane polyoxygéné / diéthylaminotrifluorosulfurane (DAST) / participation de groupement benzyle / participation de groupement amide / L-gulonolactone / 1,4-diol différemment protégé

Introduction

As inhibitors of glycosidases, new rationally designed aza-sugar mimics represent one of the most promising classes of drugs likely to alter HIV1 replication [1–3]. Such a consideration is supported by the known anti-HIV properties of deoxynojirimycin [2], *N*-butyl deoxynojirimycin [4, 5], castanospermine [6] and 6-*O*-butanoyl castanospermine [7] as well as related derivatives. Known mechanistic studies about the hydrolysis of glycosides [8] prompted us to examine the inhibitory potential of new bicyclic aza-sugar mimics based on a 9-oxaquinolizidine skeleton **1** (scheme 1, upper part). A sequence of carboxyl-assisted protonation and C–O cleavage of the perhydrooxazine function of **1** in the active site of the targeted glycosidases would afford the *N*-hydroxypropyl substituted iminium cation **2** as a potential transition state analogue of the glycosyl cation likely to inhibit these enzymes.

During the course of our synthetic studies towards the novel heterocyclic skeleton **1**, the open-chain intermediate amides **3** (Nu = OH, I, F) possessing an inverted stereochemistry at C(5) could not be prepared by chemical modification of their direct precursors **4** or mesylates **5** (scheme 1, upper part). Depending on experimental conditions and structures of the open-

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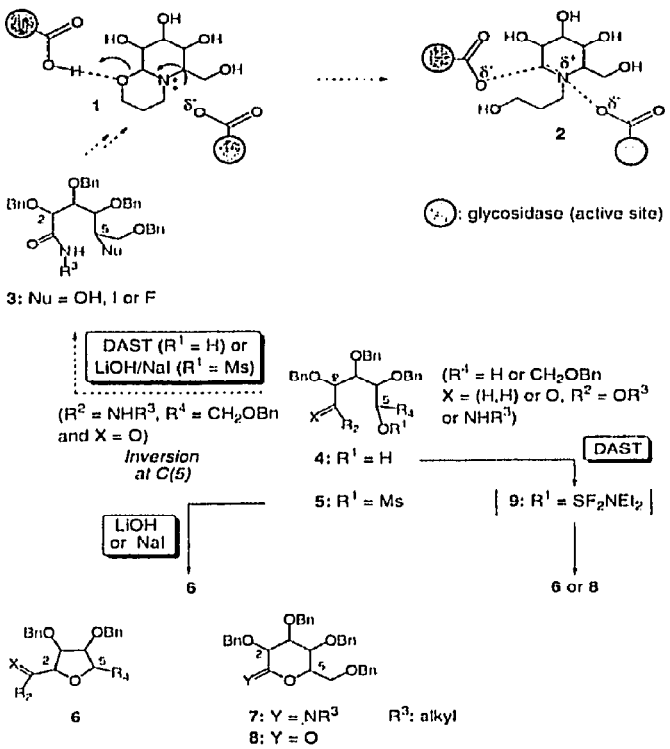


Scheme 1

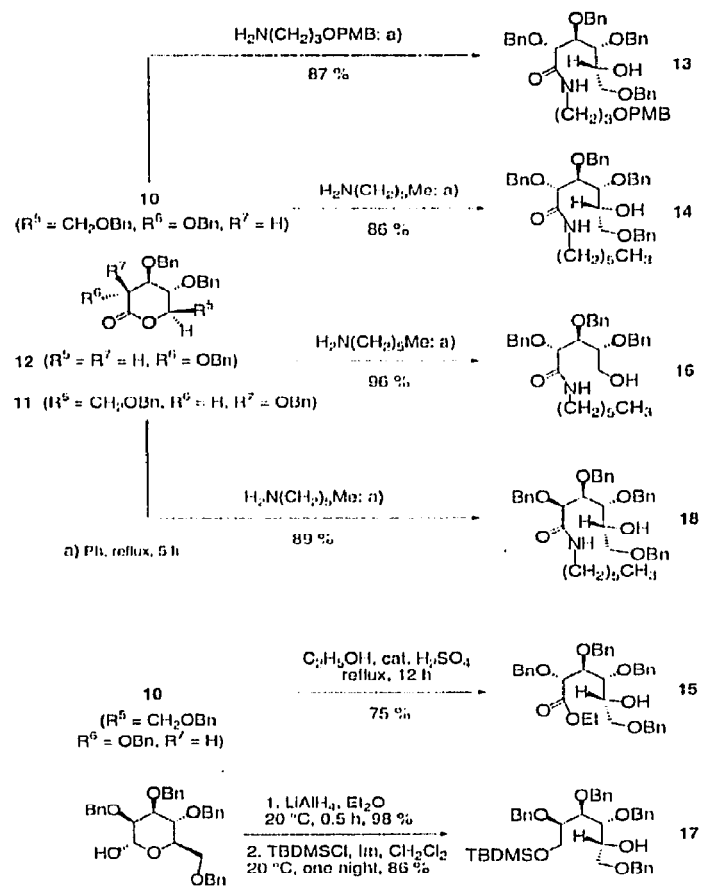
chain substrates **4**/**5**, particularly at the level of the sugar backbone, two types of intramolecular cyclizations were observed according to the chemical nature of the participating group. The nucleophilic participation of the benzyloxy at C(2) in **4**/**5** as well as the amide group in **4** can afford, respectively, the polyoxygenated tetrahydrofuran **6** or the lactone **8** (*O*-cyclization via the corresponding iminolactone **7** followed by hydrolysis). Among the conditions tried, we soon focused on two sets of experimental conditions. The first involves reaction of the mesylate **5** with one of the two reagents: LiOH or NaI (two-step cyclization from **4**, see scheme 1, lower part and table I). The second arose from an unsuccessful fluorodehydroxylation reaction performed on the precursor alcohol **4** itself using (diethylamino)sulfur trifluoride (SF_3NEt_2, DAST) [9] in CH_2Cl_2 at low temperature (one-step cyclization).

Although not directly related to our initial project, these new cyclization conditions have an interesting synthetic potential since they apply to open-chain substrates **4** or **5** allowing a *cis/trans*-stereoselective construction of highly oxygenated tetrahydrofurans of type **6**. Such complex and diverse substructures, frequently encountered in many natural products, have stimulated the search for efficient, rapid and stereoselective methods of their preparation [10].

Results and discussion

The purpose of this communication is to delineate the scope and limitations of our new conditions emphasizing particularly the stereoselective synthesis of chiral polyoxygenated tetrahydrofurans from various open-chain precursors (table I).

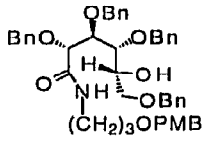
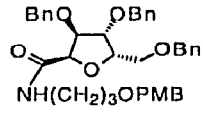
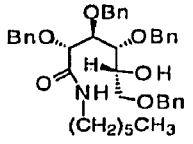
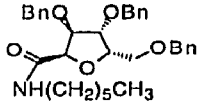
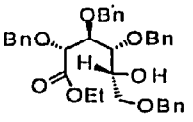
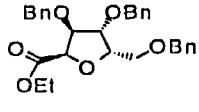
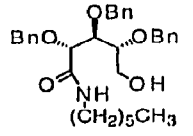
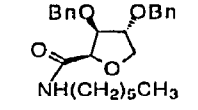
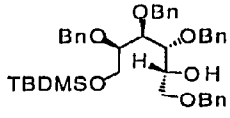
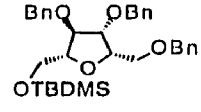
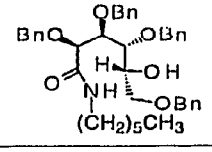
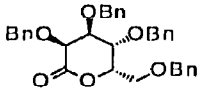
As depicted in scheme 2, precursors **13**, **14**, **16** and **18** were synthesized by aminolysis of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone/mannonolactone **10**/**11** and 2,3,4-tri-*O*-benzyl-D-xylonolactone **12** using 3-(4-methoxybenzyloxy)propylamine or hexylamine (2 equiv, benzene at reflux, 5 h, yields ranging from 75 to 96%). *trans*-Esterification of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone **10** in ethanol at reflux using catalytic H_2SO_4 afforded the benzylated ethyl ester **15** (75% yield). Additionally, 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose was submitted to a reduction reaction ($LiAlH_4$, ether, 20 °C, 0.5 h, 98%) followed by a selective silylation of the intermediate diol (TBDMSCl, CH_2Cl_2, imidazole, 20 °C, overnight, 86%) to give the silylated precursor **17**.



Scheme 2

After mesylation of **13**–**18** (MsCl, TEA/ether, 20 °C, 0.5 h, TLC control), the expected mesylates were used immediately in the cyclization promoted by LiOH (4 equiv, THF/H_2O 1:1 mixture, reflux, 2 h) or NaI (4 equiv, CH_3CN, reflux, 2 h). In parallel, **13**–**18** were reacted with DAST (1.5 equiv) in CH_2Cl_2 at −78 °C (table I).

Table I. Cyclization conditions/reagents, structures of hydroxylated precursors **13–18**, and cyclized adducts tetrahydrofurans **19–23** and lactone **24**.

Entry	*Open-chain substrate*	*Compound*	*Reagent(s)*	*Cyclization product*	*Compound*	*Yield (%, cis/trans ratio)*[d]
1		**13**	DAST[a] MsCl[b] LiOH[c]		**19**	80 (1:99) 86 (5:95)
2		**14**	DAST[a] MsCl[b] NaI[c]		**20**	59 (1:99) 82 (4:96)
3		**15**	DAST[a] MsCl[b] NaI[c]		**21**	62 (1:99) 76 (4:96)
4		**16**	DAST[a] MsCl[b] NaI[c]		**22**	78 (1:99) 78 (2:98)
5		**17**	DAST[a] MsCl[b] NaI[c]		**23**	77 (1:99) 86 (3:97)
6		**18**	DAST[a]		**24**	77 (1:99)

PMB: *p*-methoxybenzyl. [a] DAST (1.5 equiv), CH_2Cl_2, −78 °C, 2 h. [b] MsCl (1.1 equiv), NEt_3 (1.1 equiv), ether, 20 °C, 2 h. [c] LiOH (4 equiv), THF/H_2O 1:1, reflux or NaI (4.0 equiv), CH_3CN, reflux, 2 h. [d] Assay of the *cis/trans* chromatographically inseparable cyclized adducts by ^{13}C NMR. (75 MHz) at the level of at least two well-resolved resonances (the reported *cis/trans* ratio of 1:99 indicated that the other cyclic diastereomer cannot be detected).

On the basis of the best results in table I, the following may be concluded. First, the one-step cyclization (DAST[a]) or the two-step mesylation-cyclization (MsCl[b] then LiOH[c] or NaI[c]) performed on **13–17** (table I, entries 1–5) both afford good yields (59–86%) of tetrahydrofurans **19–23**, arising from an intramolecular participation of the benzyloxy group at C(2). Variable amounts of unreacted precursors (5–15%) are recovered after purification therefore providing a good mass balance.

It is particularly attractive that DAST promotes this cyclization even at −78 °C, most likely via the sulfinate **9** (see scheme 1). This fluorinating reagent must be considered as a very powerful activating agent for hydroxyl functions as already observed during a new and efficient synthesis of 2-oxazolines/thiazolines from 1,2-amido/thioamido alcohols [11, 12]. Spectroscopic (IR, high field $^1H/^{13}C$ NMR, 2D-correlations) and analytical data agree with the adduct structures depicted.

Some related cyclizations affording 2,5-substituted tetrahydrofurans by benzyloxy participation are known and result in a more or less efficient control of the *cis/trans*-2,5-stereoselectivity [13]. Furthermore, it is interesting to note that these previous observations as well as our own results emphasize the limitations encountered with the use of the benzyl protecting group especially when the functions reacting are in a 1,4-relationship.

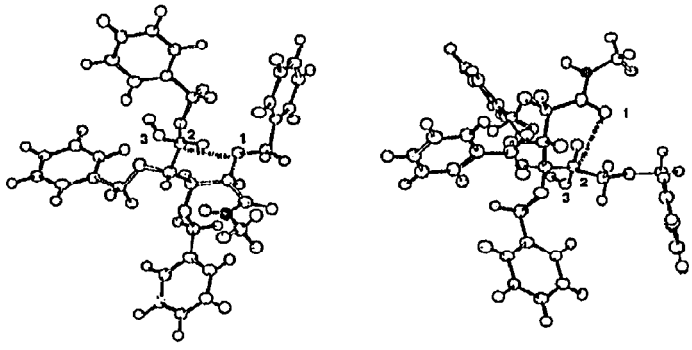
Second, whatever the experimental conditions, the isolation of **19–23** is independent of the primary/secondary nature of the activated alcohol at C(5) in the case of precursors **13–17** (entries 1–5). Additionally, an amide (entries 1, 2, 4), ester (entry 3), or a *tert*-butyldimethylsilyloxy group (entry 5) at C(1) have no influence on the cyclization since the same mode of nucleophilic participation is observed.

Third, net S_N2 type inversion of stereochemistry at C(5) in **13–15** and **17** provides the *trans*-2,5-disubstituted tetrahydrofurans **19–21** (entries 1–3) as well as *cis*-derivative **23** (entry 5) in comparable yields. Magnetization transfer (NOEDIFF experiments) between H(2) and H(5) in **23** is observed but is absent in **19**. Furthermore, although higher yielding, the two-step cyclization (NaI or LiOH) is slightly less stereoselective. High-field ^{13}C NMR signals for the carbonyl group in the inseparable mixture of *cis/trans*-adducts indicate a

90–96% diastereomeric purity as compared with a purity of at least 98% observed with the DAST-mediated cyclization.

Finally, the cyclization of **14** and **18** illustrates the two possible S_N2-type modes of participation, that is benzyloxy versus amide (entries 2 and 6) leading respectively to the tetrahydrofuran **20** and the six-membered lactone **24** (diastereomeric purity 98%) [14]. Since these open-chain precursors differ only by the absolute stereochemistry at C(2) (*gluco* versus *manno* configuration), this unexpected observation seems to indicate the involvement of two very different cyclization transition states, tentatively depicted using molecular modeling (fig 1) and easily understood as shown in scheme 3. Related to these transition states en route to lactone **24** and tetrahydrofuran **25** as a simpler methyl amide analogue of **20**, the conformations of acyclic precursors (**26**) (*gluco* configuration) and **27** (*manno* configuration) have been optimized in order to limit the number of conformational minima for these highly conformationally mobile compounds. This study has been accomplished by the following procedure.

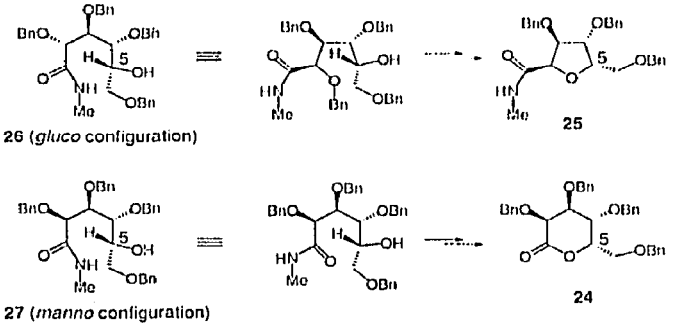
26 (*gluco* configuration) **27** (*manno* configuration)



C(2)-O(1) distance: 2.78 ÅÅ
O(1)-C(2)-O(3) angle
(dashed line): 159.3°

C(2)-O(1) distance: 3.22 Å
O(1)-C(2)-O(3) angle
(dashed line): 160.6°

Fig 1. Configurations of **26** and **27**.

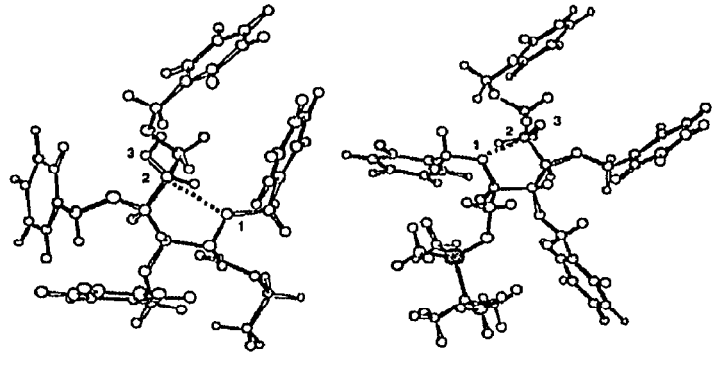


Scheme 3

Cyclic compounds **24** and **25** were minimized (MAD V 2.2 software, Oxford Molecular Ltd) using the Allinger's MM2 force field [15] and a usual minima Monte-Carlo search. Cleavage of the two bonds C(5)-O in these optimized structures without any further structural modification is followed by saturation of the opened valences by the appropriate functional group. In order to take into account potential intramolecular hydrogen bonds, we considered between unbounded atoms a term of electrostatic interaction of charge-charge type and not a dipole-dipole term as considered usually by the MM2 force field. Charges were calculated by Gasteiger's method [16]. Minimization of these open-chain structures without minima Monte-Carlo search afforded the two depicted conformational states, **26** and **27** (scheme 3), analogues of **14** and **18**.

Interestingly, the two participating groups in minimized compounds **26** (D-*gluco* configuration) and **27** (D-*manno* configuration) are suitably disposed spatially for a five- or six-membered ring cyclization (scheme 3). In particular, the atoms O(1), C(2) and O(3) involved in the cyclization are in an expected quasi-linear disposition since the calculated trajectory angles between those reacting centers are close to the ideal 180° value (**26** O(1)-C(2)-O(3) = 159.3°; and **27** O(1)-C(2)-O(3) = 160.6°) (fig 1). Moreover, following the same optimization procedure, the minimized conformations of precursors **15** and **17** indicate a five-membered ring benzyloxy participation independent of the chemical function at C(1) (entries 2, 3 and 5; fig 2). Distances C(2)-O(1) and trajectory angles O(1)-C(2)-O(3) are in the same range as the previously observed values (O(1)-C(2)-O(3)/C(2)-O(1): **15** 162.1°/2.69 Å; **17** 165.3°/2.81 Å).

15 **17**



C(2)-O(1) distance: 2.69 ÅÅ
O(1)-C(2)-O(3) angle
(dashed line): 162.1°

C(2)-O(1) distance: 2.81 Å
O(1)-C(2)-O(3) angle
(dashed line): 165.3°

Fig 2. Optimized conformations of **15** and **17**.

Conclusion

Among our two sets of experimental conditions (LiOH/NaI or DAST) for promoting the cyclization of chiral oxygenated open-chain precursors **13–18** to the corresponding tetrahydrofurans **19–23** or lactone **24**, DAST was shown to be the most promising reagent both in terms of yields (61–80%) and stereoselectivity (diastereomeric purity of cyclized adducts ⩾ 98%). Even at a temperature of −78 °C and depending on the substrate, an S_N2-type intramolecular benzyloxy or

amide group nucleophilic participation is observed following hydroxyl activation by DAST. Molecular modeling studies provide a tentative rationale to explain the different modes of cyclization in the particular case of the two acyclic precursors **14** and **18**.

Experimental section

Generalities about this section have been described elsewhere [17]. The spectra of **13–18** were obtained in $CDCl_3$ at 200 MHz (^1H NMR) and 50 MHz (^{13}C NMR) while **19–24** were characterized at 300 and 75 MHz. Analytical HPLC analyses were performed on a Waters Symmetri-C18 reverse-phase column (5 μm, 250 × 4.6 mm, t = 35 °C) by using Shimadzu 10 AS HPLC pump at 1.5 mL/min flow rate equipped with a diode-arrayed LKB 2140 detector (190–370 nm). DAST is commercially available (Janssen Chimica) and was used as received without prior purification.

Aminolysis of sugar lactones: a typical experimental procedure

The appropriate sugar lactone (4.4 mmol) and 3-[(4-methoxybenzyl)oxy]propylamine or hexylamine (8.8 mmol, 2.0 equiv) were refluxed in 15 mL of benzene under argon for 5 h. After completion of the reaction, the organic solvent was evaporated and the crude hydroxylated amide was purified by flash chromatography on silica gel affording the corresponding pure compound (elution with the appropriate solvent mixture (SM) and yields).

• *N-[3-(4-Methoxybenzyl)propyl]-2,3,4,6-tetra-O-benzyl-D-gluconamide* **13**

SM: hexane/ethyl acetate 1:1 (colorless oil, 87%).

IR (NaCl): 3 404 (ν_{OH}), 2 929, 2 863 (ν_{CH,CH_2}), 1 669 (ν_{CO}), 1 612, 1 585, 1 453 ($\nu_{C=C\ phenyl}$, ν_{CHBn}), 1 248 (ν_{CO}) cm^{-1}.

^1H NMR: δ 1.72 (q, J = 4.6 Hz, 2H), 2.95 (d, J = 3.0 Hz, 1H), 3.20–3.35 (m, 1H), 3.40–3.51 (m, 3H), 3.58–3.67 (t, J = 2.5 Hz, 2H), 3.76 (s, 3H), 3.85–3.96 (m, 2H), 4.10 (t, J = 3.2 Hz, 1H), 4.25 (d, J = 2.7 Hz, 1H), 4.31 (s, 2H), 4.51–4.72 (m, 8H), 6.84 (d, J = 8.6 Hz, 2H), 7.17–7.35 (m, 23H).

^{13}C NMR: δ 29.2, 37.4, 55.1, 68.3, 71.2, 72.7, 73.2, 73.6, 74.8, 75.5, 78.1, 79.9, 80.5, 113.7, 127.5, 127.6, 127.9, 129.3, 130.3, 136.6, 138.0, 138.1, 138.8, 159.1, 170.5.

MS (CI, NH_3): 734.0 $[MH]^+$.

Anal calc for $C_{48}H_{51}NO_8$ (733.90): C, 73.65; H, 7.00. Found: C, 73.41; H, 6.98.

$[\alpha]_D^{21}$ = +20 (c = 1.22, CH_2Cl_2).

• *N-Hexyl-2,3,4,6-tetra-O-benzyl-D-gluconamide* **14**

SM: hexane/ethyl acetate 7:3 (colorless oil, 86%).

^1H NMR: δ 0.89 (t, J = 6.0 Hz, 3H), 1.26–1.41 (m, 8H), 2.94 (d, J = 4.0 Hz, 1H), 3.13–3.32 (m, 2H), 3.63–3.71 (m, 2H), 3.88-3.91 (m, 2H), 4.10 (dd, J = 3.2 and 5.4 Hz, 1H), 4.28 (d, J = 2.9 Hz, 1H), 4.48–4.76 (m, 8H), 6.68 (m, 1H), 7.18–7.44 (m, 20H).

^{13}C NMR: δ 13.9, 22.4, 26.5, 29.3, 31.3, 39.1, 71.0, 71.3, 73.8, 74.0, 75.0, 76.3, 77.5, 80.0, 80.6, 127.6, 127.7, 127.9, 128.1, 128.2, 128.5, 136.7, 137.7, 138.1, 170.7.

Anal calc for $C_{40}H_{49}NO_6$ (639.89): C, 75.09; H, 7.72; N, 2.19. Found: C, 75.06; H, 7.72; N, 1.97.

$[\alpha]_D^{21}$ = +19 (c = 1.40, CH_2Cl_2).

Ethyl 2,3,4,6-tetra-O-benzyl-D-gluconate **15**

2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone **10** (2.40 g, 4.5 mmol) was dissolved in EtOH (15 mL) containing a catalytic quantity of concentrated H_2SO_4 (5.0 μL). The mixture was refluxed for 12 h, cooled to 0 °C, and then neutralized with solid Na_2CO_3 (3.0 g). After filtration, the medium was evaporated to give an oil which was purified by flash chromatography on silica gel deactivated by triethylamine (TEA) (hexane/ethyl acetate/TEA 60:40:0.01). Compound **15** was thus obtained as a colorless oil (1.9 g, 75%).

SM: hexane/ethyl acetate 6:4 (colorless oil).

IR (NaCl): 3 522 (ν_{OH}), 3 087, 3 062, 2 979, 2 868 (ν_{CH,CH_2}), 1 751 (ν_{CO}), 1 496, 1 454 ($\nu_{C=C\ phenyl}$), 1 365, 1 097 (ν_{C-O}) cm^{-1}.

^1H NMR: δ 1.20 (t, J = 7.1 Hz, 3H), 2.85 (d, J = 4.6 Hz, 1H), 3.61 (d, J = 4.6 Hz, 2H), 3.90–4.12 (m, 5H), 4.37 (d, J = 4.4 Hz, 1H), 4.48–4.80 (m, 8H), 7.23–7.40 (m, 20H).

^{13}C NMR: δ 13.9, 80.8, 71.0, 72.9, 73.2, 73.4, 73.5, 73.6, 78.0, 78.2, 79.5, 127.5, 127.8, 127.9, 128.2, 136.8, 137.3, 137.4, 137.8, 170.6.

MS (CI, NH_3): 602.0 $[M + NH_4]^+$.

Anal calc for $C_{36}H_{40}O_7$ (584.72): C, 73.97; H, 6.84. Found: C, 73.61; H, 6.79.

$[\alpha]_D^{21}$ = +38 (c = 0.48, CH_2Cl_2).

• *N-Hexyl-2,3,4-tri-O-benzyl-D-xylonamide* **16**

SM: hexane/ethyl acetate 7:3 (white solid, 94%).

IR (NaCl): 3 414 ($\nu_{NH\ amide}$), 3 306 ($\nu_{OH\ alcohol}$), 3 032, 2 929, 2 860 (ν_{CH,CH_2}), 1 653 ($\nu_{CO\ amide}$), [1 532, 1 496, 1 454] ($\nu_{C=C\ phenyl}$), 1 068 (ν_{C-O}), 1 028 cm^{-1}.

^1H NMR: δ 0.89 (t, J = 6.0 Hz, 3H), 1.26–1.42 (m, 8H), 2.37 (t, J = 5.7 Hz, 1H), 3.12–3.18 (m, 1H), 3.28–3.35 (m, 1H), 3.50–3.53 (m, 1H), 3.65–3.78 (m, 2H), 4.07–4.13 (m, 2H), 4.48–4.76 (m, 6H), 6.68 (t, J = 4.2 Hz, 1H), 7.28–7.34 (m, 15H).

^{13}C NMR: δ 13.9, 22.4, 26.5, 29.3, 31.3, 39.2, 61.6, 73.2, 73.7, 75.2, 79.4, 79.6, 79.7, 127.7, 127.8, 128.2, 128.5, 128.7, 138.1, 170.5.

MS (CI, NH_3): 520.0 $[MH]^+$.

Anal calc for $C_{32}H_{41}NO_5$ (519.68): C, 73.96; H, 7.96; N, 2.70. Found: C, 73.81; H, 8.21; N, 2.56.

$[\alpha]_D^{21}$ = +2 (c = 0.74, CH_2Cl_2).

1-O-(tert-Butyldimethylsilyl)-2,3,4,6-tetra-O-benzyl-D-mannitol **17**

Compound **17** was obtained by a two-step sequence of reduction/*tert*-butyldimethylsilylation from 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose. The sugar (0.20 g, 0.37 mmol) was dissolved in ethyl ether (5 mL) and treated with $LiAlH_4$ (28.0 mg, 0.74 mmol, 2.0 equiv) under argon for 0.5 h at room temperature. After completion of the reaction, the medium, after successive treatments with water (0.03 mL), 0.15 N NaOH (0.03 mL), and finally water (0.09 mL) became white. Filtration of the aluminium salts followed by evaporation of the solvents afforded an oil which was purified by flash chromatography on silica gel (hexane/ethyl acetate 3:2, colorless oil, 98% yield).

The corresponding pure diol was immediately silylated in the following manner: the diol (1.96 g, 3.6 mmol), imidazole (0.295 g, 4.3 mmol, 1.2 equiv) and TBDMSCl (0.654 g, 4.3 mmol, 1.2 equiv) were mixed together in CH_2Cl_2 (10 mL) at 0 °C and agitated overnight at room temperature. After quenching of the medium by water (10 mL), the decanted aqueous layer was extracted with ether (3 × 10 mL), filtered and concentrated. The remaining oil was purified

by flash chromatography on silica gel deactivated by TEA (hexane/ethyl acetate/TEA 90:10:0.01) affording pure **17** (colorless oil, 86%).

IR (NaCl): 3 468 (ν_{OH}), 3 063, 3 030, 2 856 (ν_{CH,CH_2}), 1 496, 1 454 ($\nu_{C=C\ phenyl}$), 1 390, 1 360, 1 328 (ν_{CH_3}), 1 098 (ν_{C-O}) cm^{-1}.

^1H NMR: δ 0.10 (s, 6H), 0.95 (s, 9H), 2.72 (d, J = 6.1 Hz, 1H), 3.61–3.63 (m, 2H), 3.64–3.91 (m, 3H), 4.00–4.10 (m, 3H), 4.43–4.81 (m, 8H), 7.19–7.32 (m, 20H).

^{13}C NMR: δ −3.7, 18.1, 25.8, 62.2, 70.2, 71.1, 71.8, 73.1, 73.5, 74.0, 78.2, 78.7, 80.0, 127.2, 127.5, 127.6, 128.0, 128.1, 128.2, 137.9, 138.4, 138.5.

Anal calc for $C_{40}H_{52}O_6Si$ (656.94): C, 73.13; H, 7.97. Found: C, 72.59; H, 7.82.

• *N-Hexyl-2,3,4,6-tetra-O-benzyl-*D*-mannonamide* **18**

SM: hexane/ethyl acetate 7:3 (white solid, 89%).

IR (NaCl): 3 417 ($\nu_{NH\ amide}$), 3 031, 2 929, 2 860 (ν_{CH,CH_2}), 1 662 ($\nu_{CO\ amide}$), [1 532, 1 497, 1 453] ($\nu_{C=C\ phenyl}$), 1 092 (ν_{C-O}), 1 028 cm^{-1}.

^1H NMR: δ 0.87 (t, J = 6.5 Hz, 3H, 1.23–1.41 (m, 8H), 3.20 (q, J = 6.5 Hz, 2H), 3.54 (d, J = 5.9 Hz, 1H), 3.65–3.67 (m, 2H), 3.85–4.19 (m, 3H), 4.38 (d, J = 2.9 Hz, 1H), 4.48–4.71 (m, 8H), 6.64 (m, 1H), 7.17–7.32 (m, 20H).

^{13}C NMR: δ 14.0, 22.5, 26.5, 29.4, 31.4, 39.1, 71.0, 71.3, 72.8, 73.4, 74.4, 74.5, 79.0, 80.2, 81.7, 127.5, 127.9, 128.0, 128.3, 128.5, 138.3, 170.2.

MS (CI, NH_3): 640.0 $[MH]^+$.

Anal calc for $C_{40}H_{49}NO_6$ (639.89): C, 75.09; H, 7.72; N, 2.19. Found: C, 74.95; H, 7.96; N, 1.95.

$[\alpha]_D^{21}$ = −4 (c = 2.34, CH_2Cl_2).

Tetrahydrofurans **19–23** *by the mesylation-cyclization sequence (two-step reaction): general experimental procedures*

• *Mesylation of the precursor alcohols* **13–17**

To the precursor alcohol (6.0 mmol) dissolved in anhydrous ether (30 mL) was slowly added TEA (6.6 mmol, 1.1 equiv) and mesyl chloride (6.6 mmol, 1.1 equiv). After 0.5 h of reaction at 20 °C, the white precipitate was filtered and the filtrate concentrated under vacuum affording a yellow oil. The mesylate, generally obtained in a quantitative yield, was of sufficient purity for the next cyclization step.

• *Cyclization of mesylates promoted by LiOH or NaI*

Each of the previously obtained mesylates (0.12 mmol) was refluxed for 2 h in the presence of LiOH (12.0 mg, 0.48 mmol, 4.0 equiv) in THF/H_2O 1:1 (5 mL) or NaI (75.0 mg, 0.48 mmol, 4.0 equiv) in CH_3CN (5 mL). After evaporation of the solvents, the crude tetrahydrofuran was purified by flash chromatography on silica gel affording the cyclized product (elution with the indicated SM). Yields and *cis/trans* ratios are reported in table I.

Tetrahydrofurans **19–23** *and lactone* **24** *by the DAST-mediated-cyclization (one-step reaction): general experimental procedure*

The precursor alcohol **13–18** (0.18 mmol) dissolved in CH_2Cl_2 (3 mL) under argon was cooled to −78 °C and slowly treated with DAST (42.0 μL, 0.28 mmol, 1.5 equiv, 1 mL CH_2Cl_2). The reaction mixture was agitated at the same temperature for 2 h then poured on 0.5 N NH_4OH (5 mL), previously cooled to 0 °C. The decanted aqueous phase was extracted with ether (3 × 15 mL), dried (anhydrous $MgSO_4$) filtered and concentrated under vacuum. The remaining oil, purified by flash chromatography on silica gel, afforded the pure cyclized product (elution with the indicated SM). Yields and *cis/trans* ratios were reported in table I.

• *(2R,3S,4R,5S)-2-({3-[(4-Methoxybenzyl)oxy]propyl}aminocarbonyl)-3,4-dibenzyloxy-5-[(benzyloxy)methyl]tetrahydrofuran* **19**

SM: pentane/ethyl acetate 1:1 (colorless oil).

IR (NaCl): 3 417 ($\nu_{NH\ amide}$), 3 054, 2 928, 2 866 (ν_{CH,CH_2}), 1 672 ($\nu_{CO\ amide}$), [1 514, 1 455] ($\nu_{C=C\ phenyl}$), 1 266, 1 095 (ν_{C-O}), 1 029 cm^{-1}.

^1H NMR: δ 1.74 (m, 2H), 3.35 (m, 2H), 3.67 (m, 3H), 3.76 (s, 3H), 3.97 (d, 1H, J = 3.3 Hz), 4.31–4.42 (m, 4H), 4.51–4.56 (m, 7H), 4.59 (d, 1H, J = 3.7 Hz), 6.85 (d, 2H, J = 8.4 Hz), 7.21–7.33 (m, 18H).

^{13}C NMR: δ 29.3, 55.5, 60.5, 68.4, 68.9, 72.5, 72.8, 73.2, 73.7, 81.2, 81.8, 82.0, 82.2, 113.9, 126.0, 127.9, 128.0, 128.6, 128.7, 129.0, 129.5, 131.1, 138.1, 159.5, 169.1.

MS (CI, NH_3): 626.0 $[MH]^+$, 643.0 $[M + NH_4]^+$.

Anal calc for $C_{38}H_{43}NO_7$ (625.77): C, 72.96; H, 6.88. Found: C, 72.69; H, 7.11.

$[\alpha]_D^{22}$ = +19 (c = 0.65, CH_2Cl_2).

• *(2R,3S,4R,5S)-2-[(Hexylamino)carbonyl]-3,4-dibenzyloxy-5-[(benzyloxy)methyl]-tetrahydrofuran* **20**

SM: hexane/ethyl acetate 4:1 (colorless oil).

IR (NaCl): 3 418 ($\nu_{NH\ amide}$), 3 030, 2 927, 2 859 (ν_{CH,CH_2}), 1 673 ($\nu_{CO\ amide}$), [1 531, 1 496, 1 454] ($\nu_{C=C\ phenyl}$), 1 075 (ν_{C-O}), 1 028 cm^{-1}.

^1H NMR: δ 0.90 (t, J = 5.8 Hz, 3H), 1.25–1.46 (m, 8H), 3.23 (m, 2H), 3.69 (ddd, J = 3.8, 6.2 and 10.0 Hz, 1H), 3.97 (dd, J = 3.8 and 2.6 Hz, 1H), 4.30 (dd, J = 2.6 and 3.4 Hz, 1H), 4.35–4.47 (m, 2H), 4.47–4.55 (m, 6H), 4.58 (d, J = 3.4 Hz, 1H), 6.70 (m, 1H, NH amide), 7.30–7.48 (m, 15H).

^{13}C NMR: δ 13.8, 22.3, 26.3, 29.4, 31.2, 38.7, 66.5, 71.7, 72.9, 73.4, 80.7, 81.3, 81.4 and 81.5 (2C), 127.5, 128.2, 137.2, 137.5, 137.6, 168.7.

MS (CI, NH_3): 532.0 $[MH]^+$, 549.0 $[M + NH_4]^+$.

HR-MS (EI) calc for $C_{26}H_{34}NO_5$ ($[M - PhCH_2]^+$): 440.2437, found: 440.243; calc for $C_{26}H_{35}NO_4$ ($[M - PhCH_2]^+$) 425.2566, found 425.257.

Analytical HPLC using MeOH/H_2O/CF_3CO_2H 80:20:0.01 as eluent (purity ≥99% at 252 and 217 nm, t_R = 18.8 min, V_e = 28.2 mL).

$[\alpha]_D^{25}$ = +34 (c = 1.15, CH_2Cl_2).

• *(2R,3S,4R,5S)-2-Ethoxycarbonyl-3,4-dibenzyloxy-5-[(benzyloxy)methyl]tetrahydrofuran* **21**

SM: pentane/ethyl acetate 4:1 (colorless oil).

IR (NaCl): 2 928 (ν_{CH,CH_2}), 1 761 ($\nu_{CO\ ester}$), [1 497, 1 454] ($\nu_{C=C\ phenyl}$), 1 099, 1 093 (ν_{C-O}) cm^{-1}.

^1H NMR: δ 1.25 (t, J = 7.0 Hz, 3H), 3.72 (m, 2H), 4.03 (d, J = 3.5 Hz, 1H), 4.11–4.23 (m, 2H), 4.30 (d, J = 4.8 Hz, 1H), 4.54–4.55 (m, 7H), 4.76 (d, J = 4.8 Hz, 1H), 7.23–7.35 (m, 15H).

^{13}C NMR: δ 14.3, 61.3, 61.3, 72.9, 73.2, 73.9, 80.4, 80.9, 81.7, 83.3, 128.0, 128.4, 128.9, 129.0, 129.4, 138.0, 138.4, 138.6, 170.0.

MS (CI, NH_3): 477.0 $[MH]^+$, 494.0 $[M + NH_4]^+$.

Anal calc for $C_{29}H_{33}O_6$ (477.58): C, 73.10; H, 6.72. Found: C, 73.13; H, 6.53.

$[\alpha]_D^{21}$ = +14 (c = 1.37, CH_2Cl_2).

• *(2R,3S,4R)-2-[(Hexylamino)carbonyl]-3,4-dibenzyloxy-tetrahydrofuran* **22**

SM: pentane/ethyl acetate 7:3 (colorless oil).

IR (NaCl): 3 422 ($\nu_{NH\ amide}$), 3 032, 2 930, 2 859 (ν_{CH,CH_2}), 1 670 ($\nu_{CO\ amide}$), [1 534, 1 497, 1 455] ($\nu_{C=C\ phenyl}$), 1 099 (ν_{C-O}), 1 063, 1 028 cm^{-1}.

^1H NMR: δ 0.87 (t, J = 6.2 Hz, 3H), 1.25–1.46 (m, 8H), 3.28 (m, 2H), 3.92 (d, J = 9.7 Hz, 1H), 4.04 (d, J = 3.8 Hz, 1H), 4.17 (dd, J = 3.8 and 9.7 Hz, 1H), 4.31 (d, J = 3.4 Hz, 1H), 4.42–4.61 (m, 5H), 6.58–6.72 (m, 1H), 7.30–7.34 (m, 10H).

^{13}C NMR: δ 14.1, 22.6, 26.9, 29.9, 31.6, 39.1, 71.2, 71.6, 73.0, 81.2, 82.2, 128.1–128.6, 166.7.

MS (CI, NH_3): 412.0 $[MH]^+$, 429.0 $[M + NH_4]^+$.

HR-MS (EI): calc for $C_{18}H_{27}NO_3$ ($[M - PhCHO]^+$): 305.1991, found 305.199.

Anal calc for $C_{25}H_{33}NO_4$ (411.55): C, 72.99; H, 8.02. Found: C, 74.88; H, 9.79.

$[\alpha]_D^{20}$ = +10 (c = 0.95, CH_2Cl_2).

• *(2R,3S,4R,5S)-2-{[(tert-Butyldimethylsilyl)oxy]methyl}-3,4-dibenzyloxy-5-[(benzyloxy)methyl]tetrahydrofuran* **23**

SM: pentane/ethyl acetate 9:1 (colorless oil).

IR (NaCl): 3 031, 2 928, 2 857 (ν_{CH,CH_2}), [1 497, 1 454] ($\nu_{C=C\ phenyl}$), 1 361, 1 254, 1 207, 1 096 (ν_{C-O}), 1 028 cm^{-1}.

^1H NMR: δ 0.06 (s, 6H), 0.90 (s, 9H), 3.57–3.79 (m, 4H), 3.95 (m, 1H), 4.05 (dd, J = 10.0 and 5.8 Hz, 2H), 4.22 (m, 1H), 4.42–4.59 (m, 6H), 7.27–7.38 (m, 15H).

^{13}C NMR: δ 16.6, 26.0, 64.1, 69.1, 71.7, 72.0, 73.6, 80.4, 83.2, 83.9, 84.8, 127.8, 128.5, 138.4, 138.9.

MS (CI, NH_3): 549.0 $[MH]^+$, 566.0 $[M + NH_4]^+$.

Anal calc for $C_{33}H_{44}O_5Si$ (548.80): C, 72.26; H, 8.02. Found: C, 72.35; H, 7.59.

$[\alpha]_D^{21}$ = +13 (c = 1.11, CH_2Cl_2).

• *2,3,4,6-Tetra-O-benzyl-L-gulonolactone* **24**

SM: hexane/ethyl acetate 75:25 (colorless oil).

IR (NaCl): 3 054, 2 872 (ν_{CH,CH_2}), 1 755 ($\nu_{CO\ lactone}$), [1 496, 1 454] ($\nu_{C=C\ phenyl}$), 1 184, 1 103 (ν_{C-O}), 737 cm^{-1}.

^1H NMR: δ 3.71 (d, J = 5.6 Hz, 2H), 3.80 (dd, J = 2.5 and 1.9 Hz, 1H), 3.97 (dd, J = 4.5 and 1.9 Hz, 1H), 4.36 (d, J = 2.0 Hz, 1H), 4.37–4.70 (m, 6H), 4.82–4.88 (m, 1H), 4.83 (d, J = 12.2 Hz, 1H), 5.10 (d, J = 12.3 Hz, 1H), 7.00–7.40 (m, 20H).

^{13}C NMR: δ 67.3, 72.8, 73.3, 73.4, 73.5, 73.6, 74.0, 75.5, 77.4, 128.4–127.8, 136.9, 137.1, 137.5, 137.6, 170.3.

MS (CI, NH_3): 539.0 $[MH]^+$, 556.0 $[M + NH_4]^+$.

Anal calc for $C_{34}H_{34}O_6$ (538.65): C, 75.82; H, 6.36. Found: C, 75.72; H, 6.41.

$[\alpha]_D^{21}$ = −53 (c = 1.14, CH_2Cl_2).

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References

1 Feizi T, Larkin M, *Glycobiology* (1990) 1, 17
2 Winchester B, Flett GWJ, *Glycobiology* (1992) 2, 199
3 Winchester B, *Biochem Soc Trans* (1992) 20, 699
4 Karpas A, Fleet GWJ, Dwek RA, Petursson S, Namgoong SK, Ramsden NG, Jacobs GS, Rademacher TW, *Proc Natl Acad Sci USA* (1988) 85, 9229
5 Karlsson GB, Butters TD, Dwek RA, Platt FM, *J Biol Chem* (1993) 268, 570
6 Saul R, Chambers JP, Molyneux RJ, Elbein AD, *Arch Biochem Biophys* (1983) 221, 593
7 Taylor D, Sunkara PS, Liu PS, Kang MS, Bowlin TL, Stanley Tyms A, *AIDS* (1991) 5, 693
8 a) Franck RW, *Bioorg Chem* (1992) 20, 77
b) Robinson KM, Rhinehart BL, Ducep JB, Danzin C, *Drugs of the Future* (1992) 17, 705
c) Kuroki R, Weaver LH, Matthews BW, *Science* (1993) 262, 2030
9 a) Middleton WJ, *J Org Chem* (1975) 40, 574
b) Hudlický M, *Org React* (1986) 35, 513
c) Markovskii LN, Pashinnik VE, in: *New Fluorinating Agents*, German L, Zemskov S, ed, Springer-Verlag, Berlin, 1989, pp 254-271
10 a) Bartlett PA, in: *Selectivity-a Goal for Synthetic Efficiency*, Bartmann W, Trost BM, ed, Verlag-Chemie, Weinheim, 1984, Vol 14, p 1
b) Boivin TLB, *Tetrahedron* (1987) 43, 3309
c) Kocóvsky P, Pour M, *J Org Chem* (1990) 55, 5580
d) Mitsunobu O, In: *Comprehensive Organic Synthesis Selectivity: Strategy & Efficiency in Modern Organic Chemistry*, Winterfeld E, ed, Pergamon Press, Oxford, 1991, Vol 6, p 1
e) Harmange JC, Figadère B, *Tetrahedron: Asymmetry* (1993) 4, 1711
11 Lafargue P, Guenot P, Lellouche JP, *Heterocycles* (1995) 41, 947
12 Lafargue P, Guenot P, Lellouche JP, *Synlett* (1995) 171
13 a) Rychnovsky SD, Bartlett PA, *J Am Chem Soc* (1981) 103, 3963
b) Amouroux R, Gérin B, Chastrette M, *Tetrahedron Lett* (1982) 23, 4341
c) Williams DR, White FH, *Tetrahedron Lett* (1985) 26, 2529
d) Bartlett PA, Ting PC, *J Org Chem* (1986) 51, 2230
e) Williams DR, White FH, *J Org Chem* (1987) 52, 5067
f) Mulzer J, Angermann A, Münch W, Schlichthörl G, Hentzschel A, *Liebigs Ann Chem* (1987), 7
g) Gyu Kim Y, Cha JK, *Tetrahedron Lett* (1988) 29, 2011
h) Ernert P, Vasella A, *Helv Chim Acta* (1991) 74, 2043
i) Walkup RD, Guan L, Woong Kim S, Soo Kim Y, *Tetrahedron Lett* (1992) 33, 3969
j) Dehmlow H, Mulzer J, Seilz C, Strecker AR, Kohlman A, *Tetrahedron Lett* (1992) 33, 3607
k) Fowler PA, Haines AH, Taylor RJK, Chrystal EJT, Gravestock MB, *J Chem Soc Perkin Trans 1* (1993) 1003
l) Martin OR, Yang F, Xie F, *Tetrahedron Lett* (1995) 33, 47
m) Yang BH, Jiang JQ, Ma K, Wu HM, *Tetrahedron Lett* (1995) 33, 2831
14 a) Toshimitsu A, Terao K, Uemura S, *J Org Chem* (1987) 52, 2018
b) Meng Q, Hesse M, *Helv Chim Acta* (1991) 74, 445
c) Wuts PGM, Ritter AR, Pruitt LE, *J Org Chem* (1992) 57, 6696
d) Kitagawa O, Hanano T, Hirata T, Inoue T, Taguchi T, *Tetrahedron Lett* (1992) 33, 1299
e) Engman L, *J Org Chem* (1993) 58, 2394
f) Schneider H, Sigmund G, Schricker B, Thirring K, Berner H, *J Org Chem* (1993) 58, 683
15 Allinger NL, *J Am Chem Soc* (1977) 99, 8127
16 Gasteiger J, Marsili M, *Tetrahedron* (1980) 36, 3219
17 a) Quirosa-Guillou C, Lellouche JP, *J Org Chem* (1994) 59, 4693
b) Lafargue P, Dodi A, Ponchant M, Garcia C, Le Cavorsin M, Pujol JF, Lellouche JP, *Bioorg Med Chem* (1994) 2, 827